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PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,458	WELLER ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11,15-17 and 19-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11,15-17 and 19-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on November 15, 2005.

Preliminary Remark

Claims 4, 12-14, and 18 have been canceled.

Claims 1-3, 5-11, 15-17, 19-27 are pending and are under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term, "the different analyte molecules" (in step a). It is unclear whether the different analyte molecules are referencing "the different substantially uncharged oligomeric analyte molecules" or other analyte molecules which could be present.

Claims 2-27 are indefinite by way of their dependency on claim 1.

Claim 10 is indefinite for reciting the term, "said analysis." Neither claim 10, nor its parent claims recite that an analysis is being done. While the parent claims are drawn to a method, the method is drawn to separating a population of duplexes, but does not result in an "analysis" of anything.

Claim 15 is indefinite for reciting the phrase, "charge bearing support." While claim 1 contains the limitation, "charge bearing separation medium," such is not the same as a charge bearing support. Thus, antecedent basis is insufficient for the limitation of claim 15.

Claim Rejections - 35 USC § 102

The rejection of claims 1-6, 10, 15, 19, 20, 23-24, and 26-27 under 35 U.S.C. 102(b) as being anticipated by Celebuski (U.S. Patent No. 5,932,413, issued August 3, 1999), made in the Office Action mailed on July 15, 2005 is withdrawn in view of the Amendment received on November 15, 2005.

Necessitated by Amendment

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, 10, 15-17, 19, 20, 23, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Fuchs et al. (WO 97/12995, published April 10, 1997).

Preliminarily, the instant claims use the term, "probe" and "analyte." While the term, "analyte" is commonly reserved for that which is being assayed for, and the term, "probe," for an agent that is responsible for assaying for the analyte, the terms are not exclusively limited to these definitions. In fact, they are interchangeably used (as in the instant claims) and in other publications, such as that of Affymetrix®, which often refer to the labeled, fragmented cDNAs (or cRNAs) as "labeled probes."

Fuchs et al. disclose a method of separating a population of duplexes (formed between PNA and DNA), comprising one of a population of different, substantially uncharged oligomeric analyte

molecules (PNA molecules; page 3, lines 28-29; wherein PNA is disclosed as being uncharged, *see* page 7, lines 26-27 and page 10, lines 2-3; hence at least 90% uncharged) and a specific probe molecule (DNA or RNA; *see* page 7, line 26; wherein DNA/RNA are negatively charged; *see* page 7, lines 26-27), the method comrprising:

a) applying to a charge-bearing separation medium mixture (*i.e.,* electrophoretic medium; *see* page 10, line 2, 14, and 22; page 12, lines 25-26) of (i) the different substantially uncharged PNAs (*see* page 4, lines 22-25, in the phrase, "at least two PNA probes are labeled, each of which hybridizes with a different target sequence, if present, to form a detectable complex") and (ii) the specific DNA/RNA molecules (*see* page 4, lines 23-25, in the phrase, "[t]he target sequences maybe present on the same DNA segment or separate DNA segments..."[1]), under conditions such that the probe forms stable duplexes with a plurality of or all of the different PNA molecules (page 4, lines 15-16; page 7, lines 22-26), thereby forming a plurality (at least two) of different probe-analyte duplexes, which differ from each other with respect to the presence, length or positions of an unhybridized portion of the DNA/RNA molecules[2]; and

b) separating said different probe-analyte duplexes from each other (page 12, lines 21-26) and from single stranded PNA within the medium (page 10, lines 17-28), thereby clearly anticipating claim 1.

With regard to claims 2 and 5, PNA molecules of Fuchs et al. are disclosed as being complementary to a nucleic acid sequence (page 10, lines 26-27) comprising a gene of interest (or selected sequence; *see* page 10, line 30); deletion mutants (*see* page 31, lines 7-8); substitution variant

[1] Different PNAs for the same DNA segment would necessarily meet "a specific probe molecule"
[2] Page 4 of Fuchs et al. clearly states that the PNA hybridizes to a different portion of the DNA, which would inherently result in the formation of duplexes which differ from each other with respect to the presence, length, or positions (see also page 26, lines 3-5; page 30, lines 11-13 for this inherency).

(*see* page 32, lines 22-23), etc. With regard to claim 6, the length of PNA matches the length of the desired portion of the sequence (*see* page 32, length of the wild-type probe and mutant probe).

With regard to claim 3, the mutant PNA oligonucleotide molecule comprises a mutation at its 8^{th} nucleotide position.

With regard to claim 10, the PNA mutant oligonucleotide comprises a mutation within its subregion (*see* page 32, in the mutant probe: Flu-oo-CTTTCCTTCACTGTT-NH_2 (mutation underlined)).

With regard to claims 15 and 16, Fuchs et al. explicitly disclose that the separation medium (or charge bearing support) can be electrophoresis, chromatography, mass spectrometry, or particularly a perfusion chromatography medium, i.e., POROS® available from PerSeptive Biosystems, Inc. (page 12, lines 24-29). It is well known that electrophoretic separation (electrophoresis) involves application of electric field between opposing boundaries of the electrophoretic gel, wherein the negatively charge DNA migrates toward the positive end.

With regard to claim 17, Fuchs et al. also discuss the modification of pH gradient in the electrophoretic medium (page 13, lines 7-10; page 14, lines 8-16).

With regard to claims 19 and 20, Fuchs et al. are explicit in stating that PNAs, "do not have a charge." (page 7, line 27).

With regard to claim 23, the PNAs are duplexed with DNA (page 7, lines 25-26; page 9, lines 21-22).

Therefore, Fuchs et al. clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuchs et al. (WO 97/12995, published April 10, 1997) in view of Cummins et al. (U.S. Patent No. 5,874,213, issued February 23, 1999).

The teachings of Fuchs et al. have already been discussed above.

Fuchs et al. do not explicitly teach that the probe (or DNA target) includes a sequence complementary to an N-1 deletion variant (claim 7), or that the probe has a length equal to said N-1 deletion variant (claim 8), or that the probe hybridizes only to N-1 deletion variant (claim 9), or that the population contains analyte molecules (PNAs) which are N-1 deletion variants (claim 11).

Cummins et al. disclose a method of separating duplexes formed between a 20-mer PNA and 18-mer DNA, 19-mer DNA, and 20-mer DNA, wherein the artisans evidence a clear separation among the three duplexes via capillary gel electrophoresis (CGE; *see* column 14, lines 44-45, and 62-67; column 15, lines 39-41).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fuchs et al. with that of Cummins et al., thereby arriving at the claimed invention for the following reasons.

It should be noted that DNAs are composed of double strands, each being complementary to each other. Hence, DNAs having deletion sequences, particularly, N-1 deletion, would have one strand (sense strand) having a complementary sequence to the other strand (antisense strand).

The present issue is the fact that Cummin et al. duplexes a single PNA probe (20-mer) with a 20-mer DNA; 19-mer DNA (N-1 variant); and 18-mer DNA (N-2 variant); while the instant claims are drawn to the reverse scenario, that is, duplexing N-1 deletion variant probe (DNA) with one of a population of different, substantially uncharged oligomeric analyte molecule (*i.e.,* PNA), wherein, for example, the different PNAs hybridizes only to the N-1 deletion variant.

Whether the claimed reverse scenario (than that which is disclosed by Cummins et al.) is *prima facie* obvious over the combination of the teachings of Fuchs et al. and Cummins et al. is based on whether one of ordinary skill in the art would have had a reasonable expectation of success at the time the invention was made[3].

It is clear from both Cummins et al. that duplexes formed between a fixed oligomer and complementary oligomers of varying lengths (18-mer, 19-mer, and 20-mer) are clearly distinguished from each other via electrophoretic separation. The separation is achieved, in part[4], by the differences in the sizes of the duplexes. Hence, one of ordinary skill in the art would have had a clear expectation of success at detecting a N-1 deletion variant DNA via use of PNAs of varying lengths, as one of ordinary skill in the art would have clearly expected that the differences in the sizes of the formed DNA/PNA duplexes would have resulted in different separation speed and pattern.

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[3] MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success.

[4] While the enhancement of the separation is achieved via net negative charges of the duplexes, the separation of the duplexes are also facilitated by the differences in the sizes of the duplexes formed between N, N-1, and N-2 complementary sequences and the 20-mer PNA.

This fact is further clear in instant claims 2 and 3, which allows the uncharged analyte molecules (i.e., PNAs) to comprise deletion, insertion, or mutation containing one of deletion, insertion, or mutation. A duplex formed between a specific DNA and a PNA of 20-mer (for example, a perfect match) and a PNA of 21-mer (comprising an insertion) would not have any differences in the net charge[5]. Hence, the separation of the two duplexes would only be facilitated by their differences in duplex size.

As the art of separating nucleic acid duplexes based on their size is well known in the art, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at employing varying lengths of PNAs for the purpose of detecting an N-1 deletion DNA variant.

Therefore, the invention as claimed is prima facie obvious over the cited references.

Claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuchs et al. (WO 97/12995, published April 10, 1997) in view of Ecker et al. (U.S. Patent No. 5,986,053, issued November 16, 1999).

The teachings of Fuchs et al. have already been discussed above.

Fuchs et al. do not explicitly teach that the DNA be labeled instead of the PNAs.

Ecker et al. disclose a gel-shift motility assay, which involves hybridization of PNA molecules to DNA molecules, thereby forming PNA:DNA duplexes, wherein the DNA molecules are labeled (column 14, lines 38-41; column 35, lines 23-29).

[5] The net charge of the duplex (PNA:DNA) is solely from DNA since PNA molecules do not have any charge.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fuchs et al. with the teachings of Ecker et al., thereby arriving at the claimed invention for the following reasons.

The case for *prima facie* obviousness is established based on whether one of ordinary skill in the art would have had a reasonable expectation of success at labeling the DNA molecule rather than labeling the PNA molecule, so as to detect the DNA:PNA duplex.

The gel-shift assay, as disclosed by Fuchs et al. and Ecker et al., involves the detection of the DNA:PNA duplexes, wherein the detection is achieved by a label present on the duplexes. Whether the label was present of the PNA of the duplex or the DNA of the duplex would not have mattered, so long as the duplex had a detectable label. Based on the teachings of Ecker et al., one of ordinary skill in the art would have had a clear expectation of success at labeling the DNA instead of PNA, and that such modification would not have produced a negative effect on the detection of the label duplexes (i.e., detectability), as evidenced by the success of the assay of Ecker et al.

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuchs et al. (WO 97/12995, published April 10, 1997) in view of Iversen (U.S. Patent No. 6,365,351 B1, issued April 2, 2002).

The teachings of Fuchs et al. have already been discussed above.

Fuchs et al. do not explicitly disclose that the uncharged oligomeric analyte are morpholino oligomers.

Iversen discloses a morpholino oligomer, which is explicitly disclosed as being uncharged (column 11, lines 25-27), wherein the artisan employs PMO which is defined as having phosphodiamidate morpholino oligomers (column 4, lines 54-55).

Iversen discloses an oligo:RNA heterduplex assay, wherein a duplex between an oligonucleotide which is PMO (i.e., uncharged; *see* column 18, lines 41-45) and an RNA (which is charged) is formed and detected by size separation via gel electrophoresis (column 18, lines 46-59).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fuchs et al. with that of Iversen, thereby arriving at the claimed invention for the following reasons.

Iversen discloses the primary advantage of employing morpholino oligomers in a "gel-shift" assay, the assay involving size separation of duplexes, wherein the duplexes are formed between a charged nucleic acid and a nucleoside analog which is uncharged, particularly morpholino oligonucleotides:

> "The important chemical properties of a morpholino-based subunits are the ability to be linked in a polymeric form by stable, uncharged backbone linkages, and the ability of the polymer so formed to hybridize with the complimentary-base target nucleic acid, including target RNA, with high affinity." (column 10, lines 63-67).

Hence, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Fuchs et al. with the teachings of Iversen, for the explicitly stated advantage of employing oligomers which are highly specific for their target nucleic acid. One of ordinary skill in the art would have been motivated to employ oligomers which are highly specific for their target nucleic acid, as the method disclosed by Fuchs et al. is dependent on the ability of the oligomer to form a highly specific duplex with its target nucleic acid, the desire of which has been expressed by Fuchs et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Applicants are reminded that the instant claims do not recite the limitation "positively charged solid phase." (see page 9, Response)

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be

sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
2/13/2006

YOUNG J. KIM
PATENT EXAMINER

yjk